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| 10/581,413 | 06/23/2006 | Kenya Shitara | 00005.001295 | 1999 |
| 5514 7590 10/17/2007 FITZPATRICK CELLA HARPER & SCINTO 30 ROCKEFELLER PLAZA NEW YORK, NY 10112 | | | | |
| | | | EXAMINER WEN, SHARON X | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|-------------------------------|--------------------------------|--|
| Office Action Summary | Application No. 10/581,413 | Applicant(s) SHITARA ET AL. | |
| | Examiner Sharon Wen | Art Unit 1644 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-4 and 7-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5 and 6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment, filed 06/02/2006, has been entered.
Claim 2 has been canceled.
Claims 1 and 3-26 are pending.

Election/Restrictions

2. Applicant's election of Group II drawn to a process of treating tumor and species of 1) positions 13-25 of amino acid sequence of SEQ ID NO: 1 to which the antibody binds; 2) SEQ ID NOs: 5-7 for CDR's 1-3 of heavy chain variable region; 3) SEQ ID NOs: 8-9 for CDR's 1-3 of light chain variable region; 3) G-CSF as the pharmaceutically active agent; and 4) KM8761 hybridoma cell line in the reply filed on 08/27/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-4 and 7-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic claim.

Claims 5-6 are currently under examination as they read on a process of treating tumor comprising administering a medicament comprising an antibody that specifically binds chemokine receptor 4 (CCR4).

3. In response to Applicant's species election of KM8761 hybridoma, it is acknowledged that the elected species is not found in the specification as indicated by Applicant, in Response to Election Requirement, filed 08/27/2007.

Applicant is invited to indicate the corresponding sequences of CDRs of the antibody produced by KM8761.

Priority

4. The effective priority date for claims 5-6 is deemed the effective filing date of the international application, PCT/JP04/18430, i.e. 12/03/2004.

Applicant's claim for foreign priority is acknowledged. Certified copies of foreign priority applications, 2003-406590 and 2004-155141, submitted under 35 U.S.C. 119(a)-(d), have been placed of record in the file. The support for Applicant's claim for foreign priority cannot be determined because applications 2003-406590 and 2004-155141 are in Japanese and no certified translation has been provided.

Applicant is invited to amend the first line of the specification to reflect Applicant's claim for domestic priority.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on 05/17/2007 is acknowledged and being considered by the examiner.

Specification

6. Applicant is requested to review the application for the spelling errors, use of trademarks, embedded hyperlinks and/or other form of browser-executable code.

Trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference.

Claim Objections

7. Claims 5-6 are objected to because of the following informalities:

A) The instant claims depend from non-elected claims, claims 4 or 7-20, which have been withdrawn from further consideration.

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Applicant is required to amend the instant claims to recite the limitations of the non-elected dependent claim.

For examination purpose, claims 5-6 reads on process of treating tumor comprising administering a medicament of any one of claims 4 and 7-20.

B) The abbreviated terms recited in claim 8, "TARC" and "MDC", should be spelled out first time appearing in the claims.

C) Applicant is reminded that any amendment must point to a basis in the specification as not to add any New Matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 5-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) The following Grounds of Rejection pertain to an antibody with fewer than all 6 CDRs.

Claims 5-6 recite three CDRs of the heavy chain variable region or the light chain variable region (see dependent claims 17 or 20).

The breadth of the instant claims encompasses an anti-human CCR4 antibody with only three CDRs found in either the heavy chain or the light chain.

The specification discloses that anti-human CCR4 antibody with complete viable domains with six CDRs for both heavy chain and light chain (e.g. see Examples on pages 33-38 of the instant specification).

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However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various amino acids sequences recited in the instant claims. A person skill in the art would not be able to predict which additional CDRs are to be paired together to form a functional anti-human CCR4 antibody.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function.

For example Rudikoff et al. (PNAS 1982 Vol 79, pages 1979-1983) teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see entire document, particularly page 1979).

Further, The state of the art at the time the invention was made recognizes even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function.

For example, Rader et al. (PNAS. 1998. 95:8910-8915) teach in vitro selection and evolution of antibodies derived from phage display libraries by pairing either heavy or light chain of the rodent antibody with human polypeptide library for antibody humanization is unpredictable, and certain antibodies cannot be humanized using this approach; and in addition, antibodies consisting of the same heavy chain paired with light chains that differ in light chain CDR3 and elsewhere in VL can obtain undesired feature of binding different epitopes of the same antigen (see entire document, particularly Discussion on pages 8914-8915). Rader et al.

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methods do not result in an antibody solely by keeping CDR3 in the VH defined and randomizing the rest of the VH and VL domain.

Furthermore, Rader et al. conclude that therapeutic antibodies that are unreactive to the antiidiotypic response would allow therapy to continue and introduction of modest changes within the variable domain of an antibody can dramatically alter its reactivity to an antiidiotypic response.

Therefore, it is unlikely that the antibodies as defined by the claims, which contain only three CDR3 in either heavy or light chain would have the required binding function and functional limitations such as specifically binds an extracellular region of human CCR4. The specification provides insufficient direction or guidance regarding how to produce antibodies as broadly defined by the claims other than the antibody with all six CDRs for both heavy and light chain. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In view of the quantity of experimentation necessary, the limited working example, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention using the antibody with only three CDRs.

B) The following Grounds of Rejection pertain to treating tumor.

Claims 5-6 are directed a process of treating tumor specially, hematopoietic organ tumor comprising administering an anti-CCR4 antibody. The specification provides enabling disclosure for showing the anti-CCR4 human chimeric antibody KM2760 is cytotoxic to mouse tumor cells that have been transformed to express human CCR4 in vitro (see Example 1 on pages 33-36) and reduced the volume of grafted tumors in mice when administered with G-CSF (see Example 6 on pages 44-47). The specification does not provide sufficient *in vivo* or *in vitro* evidence showing the composition comprising the anti-CCR4 antibody and G-CSF to treat all tumors as broadly claimed in claim 5, nor does the specification provide sufficient enabling evidence for treating hematopoietic organ tumor which reads broadly on leukemia, Hodgkin's disease or non-Hodgkin's as disclosed on page 26 of the specification.

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Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering the antibody. The specification does not teach how to extrapolate data obtained from in vitro inhibition of Th2 cytokine production (see page 77 of specification) to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the antibody exemplified in the specification or the method of treating using the antibody, encompassed by the claims.

According to *The Merck Manual of Diagnosis and Therapy*, the treatment for Hodgkin's disease, a species of hematopoietic organ tumor disclosed in the instant specification, is complex and depends on the precise stage of the disease and often followed by complications of treatment. (*The Merck Manuals Online Medical Library*, [online]. Whitehouse Station, NJ: Merck Research Laboratories, 2006-2007. [retrieved on 10/10/2007]. Retrieved from the Internet: < URL: <http://www.merck.com/mmpe/print/sec11/ch143/ch143b.html> >. Hodgkin lymphoma, pages 1-5, in particular, see sections under **Prognosis and Treatment** and **Complications of Treatment**). However, the instant disclosure does not provide sufficient in vitro or in vivo evidence showing the administration of anti-CD4 antibody can counter-act the cause or the manifestation of Hodgkin's disease as defined by *The Merck Manual of Diagnosis and Therapy* in order to treat the disease.

Moreover, Applicant has not enabled one of skill in the art to use the antibody of the instant claims to treat a broad genus of diseases encompassed by hematopoietic organ tumor which include various species such as leukemia disclosed in the instant specification (see page 26 of the specification). According to *The Merck Manual of Diagnosis and Therapy*, the etiology and pathophysiology of leukemia include abnormal proliferation, clonal expansion, and diminished apoptosis (programmed cell death) that lead to replacement of normal blood elements with malignant cells (*The Merck Manuals Online Medical Library*, [online]. Whitehouse Station, NJ: Merck Research Laboratories, 2006-2007. [retrieved on 10/10/2007]. Retrieved from the Internet: < <http://www.merck.com/mmpe/print/sec11/ch142/ch142a.html> >. Leukemia, see pages 1-4). However, the instant disclosure does not provide sufficient *in vivo* evidence showing the administration of an anti-CCR4 antibody can counter-act the cause or the manifestation of leukemia as defined by *The Merck Manual of Diagnosis and Therapy* in order to treat the disease.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Immunomodulation is much easier to achieve under such controlled conditions than that experienced in the human disorders or diseases such as Hodgkin's disease and leukemia targeted by the claimed invention (see pages 26 of the instant specification).

The instant application provides insufficient guidance and instruction on the necessary steps one of skill would need to administer the peptide and achieve the intended results, i.e. treating hematopoietic organ tumor. In view of the unpredictability of the art and insufficient working examples provided by Applicant of administering an anti-CCR4 antibody for therapy, it would require undue amount of experimentation for a skilled artisan to practice the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

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C) The following Grounds of Rejection pertain to biological deposit.

Claims 5-6 are rejected for failing to enable one of skill to make or use the claimed invention.

It is apparent that KM2160 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line or hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Although applicant has deposited hybridoma clone KM2160 on August 12, 2004 with the International Patent Organism Depository, National Institute of Advanced Industrial Science and Technology, AIST Tsukuba Central 6, 1-1, Higashi 1-chome Tsukuba-shi, Ibaraki, Japan, and accorded Accession Number FERM BP-10090 (see page 11 of the specification) there appears no assurances indicated above. Applicant's provision of these assurances would obviate this rejection.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Shitara et al. (US 2003/0175273 A1, see entire document).

Shitara et al. teach a method comprising administering a medicament comprising a combination of a recombinant anti-CCR4 antibody and a pharmaceutically active agent, wherein the agent is G-CSF (see, e.g., paragraphs [0159]-[0163] and [0229]-[0251]).

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In particular, the reference antibody appears to be the same or nearly the same antibody as the instant application with identical CDRs (see paragraphs [0049]-[0050] and SEQ ID NOs: 1-3 and 5-7). In addition, the reference teaches the antibody to be is a human chimeric antibody or a human CDR-grafted antibody (see abstracted and paragraph [0310]). Furthermore, the reference teach a monoclonal antibody produced by hybridoma KM2160 (see paragraph [0255]-[0258]).

Given the same or nearly the same antibody, the reference antibody would inherently bind to positions 13 to 25 of amino acid of CCR4 of SEQ ID NO: 1 and would not have an activity of inhibiting binding of TARC or MDC as a CCR4 ligand to CCR4.

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Shitara et al. is silent on treating tumor. However given the reference teaches the antibody has cytotoxic activity against CCR4-expressing cell, and that tumor cells express high at high frequency in leukemia/lymphoma cells as evidence by the instant specification (see page 1, last sentence), one of ordinary skill in the art would have immediately envisaged the same method as taught by the reference would also treat leukemia/lymphoma.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See *Bristol-Myers Squibb Company v. Ben Venue Laboratories* 58 USPQ2d 1508 (CAFC 2001).

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Wen whose telephone number is (571) 270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharon Wen, Ph.D.

Patent Examiner

October 11, 2007


PHILLIP GAMBEL, PH.D. JD
PRIMARY EXAMINER



